Title: Are myocardial infarction-associated single nucleotide polymorphisms associated with ischemic stroke?

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Abstract

Background and Purpose — Ischemic stroke (IS) shares many common risk factors with coronary artery disease (CAD). We hypothesized that genetic variants associated with myocardial infarction (MI) or CAD may be similarly involved in the etiology of IS. To test this hypothesis, we evaluated whether single nucleotide polymorphisms (SNPs) at 11 different loci recently associated with MI or CAD through genome-wide association studies were associated with IS.

Methods — Meta-analyses of the associations between the 11 MI-associated SNPs and IS were performed using 6,865 cases and 11,395 controls recruited from 9 studies. SNPs were either genotyped directly or imputed; in a few cases a surrogate SNP in high linkage disequilibrium was chosen. Logistic regression was performed within each study to obtain study-specific betas and standard errors. Meta-analysis was conducted using an inverse variance weighted approach assuming a random effect model.

Results — Despite having power to detect odds ratio of 1.09-1.14 for overall IS and 1.20-1.32 for major stroke subtypes, none of the SNPs were significantly associated with overall IS and/or stroke subtypes after adjusting for multiple comparisons.

Conclusions — Our results suggest that the major common loci associated with MI risk do not have effects of similar magnitude on overall IS, but do not preclude moderate associations restricted to specific IS subtypes. Disparate mechanisms may be critical in the development of acute ischemic coronary and cerebrovascular events.

Introduction

Ischemic strokes (IS) comprise 87% of all strokes[1]. Nearly 800,000 individuals in the US experience a stroke each year, making stroke one of the leading causes of serious, long-term disability in developed countries [1, 2]. The tendency of stroke to aggregate within families implies a genetic etiology, although few genetic variants have as yet been unequivocally linked to the common forms of IS.

Some of the difficulty in identifying stroke susceptibility genes may arise from heterogeneity within the stroke phenotype, making it imperative to carry out genetic studies within specific subtypes of IS. IS syndromes can, in fact, be recognized by experienced clinicians with a high degree of inter-rater agreement [3]. The major categories, which are based upon the presumed stroke mechanism, include atherosclerotic (i.e. large artery) stroke, cardioembolic stroke, and small vessel (lacunar) stroke. Given disparate mechanisms, it is likely that different risk alleles would contribute to these different stroke subtypes. Previous studies showing that a family history of stroke is more common in younger compared to older age of onset strokes [4-6] raise the additional possibility that the genetic contribution to stroke may differ by age of onset.

IS shares many risk factors with myocardial infarction (MI) and coronary artery disease (CAD), including smoking and high blood pressure. The possibility that common susceptibility genes might predispose to both IS and MI/CAD prompted us to examine whether genetic variants previously associated with MI/CAD might also be associated with IS. To address this hypothesis, we evaluated whether DNA sequence variants at 11 different loci recently associated with MI or CAD through genome-wide association (GWA) studies were also associated with IS. Our analysis included 6,865 IS cases from 9 different studies, allowing us to test whether the

genetic variants were associated not only with overall IS, but also with the major IS subtypes and with age of stroke onset.

Materials and Methods

Study Populations

This analysis includes 6,865 IS cases and 11,395 controls from 9 different studies: Australian Stroke Genetics Collaborative (ASGC), Bio-Repository of DNA in Stroke (BRAINS), Besta Cerebrovascular Diseases Registry (CEDIR), Genes Affecting Stroke Risk and Outcomes Study (GASROS), Genetics of Early Onset Stroke (GEOS), Graz Stroke Study (GRAZ), Ischemic Stroke Genetics Study and Siblings with Ischemic Stroke Study (ISGS/SWISS), Risk Assessment of Cerebrovascular Events (RACE) and the Vitamin Intervention for Stroke Prevention (VISP) study. All stroke cases, except those from VISP study, were adjudicated for ischemic stroke subtype using the original TOAST system[3], which assigns each case to one of the following categories: cardioembolic, large artery, small vessel, other known causes and undetermined causes. Controls free of stroke were selected based on study-specific criteria. For this report, cases and controls with a known history of MI were excluded from the analyses. Details of the study designs for each participating study are included in the Supplemental Method (http://stroke.ahajournals.org).

All participating studies were conducted with the consent of study subjects and were approved by the Institutional Review Board in each institution.

SNP selection

SNPs shown previously to be associated with MI or CAD in Caucasians were identified through a review of genome-wide association studies published before May 2010. MI/CAD-associated SNPs reported in these previously published GWA studies were selected for inclusion in this study only if their associations with MI/CAD reached genome-wide significance ($P<5x10^{-8}$) and were replicated in at least one large independent Caucasian cohort. Based on these criteria, we identified 11 loci from nine chromosomes that were consistently associated with MI/CAD (see Table 1)[7-13].

Genotyping and Imputation

The 11 MI-associated SNPs selected for inclusion in this study were genotyped by existing commercial genome-wide SNP platforms, KASPar SNP array (KBioscience, Herts, UK) and/or by Taqman assays (Applied Biosystems, Foster City, USA). For SNPs that were not directly genotyped, genotypes were obtained either via imputation or the targeted SNP was replaced by a surrogate SNP that was in high linkage disequilibrium (LD $r^2 > 0.8$) with the target SNP. A detailed description on the genotyping and imputation methods for each participating site is provided in Supplemental Table S1.

Statistical Analysis

Site-specific logistic regression analysis was performed to test for associations of each individual SNP with IS under an additive model, and then site-specific beta coefficients (β) and standard errors (S.E.) were pooled in meta-analyses. A genotype risk score was also computed for each individual by summing the number of MI/CAD-risk alleles across each of the 11 loci (score 1). Each SNP was given equal weights rather than weights based on their effect sizes (β)

for MI/CAD in the risk score calculation given that we do not know the effects of these SNPs on stroke and the assumption that they would have similar effects on stroke as they do on MI seems unjustified. Additionally, we computed a genotype risk score that summed the number of MI/CAD-risk alleles across 10 loci, excluding SNP rs4977574 on chromosome 9, because SNPs near this locus have previously been reported to be associated with large artery stroke (score 2)[14]. Each genotype risk score was used as a continuous independent variable in the logistic regression model to obtain the joint additive effects of all MI/CAD-associated SNPs on the risk of IS. The β of the genotype risk score represents the increase in log odds of stroke associated with having one additional MI/CAD-risk allele. The GRAZ study was not included in the score analyses because three of the 11 SNPs were not genotyped directly and could not be imputed with acceptable quality scores (rs6725887, rs9818870 and rs9982601). Overall, about 35% of the individuals in whom one or more SNPs were not genotyped or imputed were removed from the genotype risk score analysis. For ease of result interpretation, all odds ratios were designated with the previously published non-risk allele as the reference so that the odds ratio reflects the effect of the MI-associated risk allele. Association analyses were adjusted for study-specific covariates (e.g. age, sex and population structure) (see Supplemental Table S2).

Meta-analysis was performed using a variance-weighted approach assuming a random effect model (DerSimonian & Laird method)[15], which takes heterogeneity of the genetic effects across studies into account. Between-study heterogeneity was estimated using Cochran's Q statistic, which is the summation of the squared weighted difference between the study-specific effect and the overall effect size (estimated by the fixed effect), as well as I^2 statistics, which represent the percent of total variation across studies due to heterogeneity after accounting for variability due to chance. All meta-analyses were performed using the *metan* module

implemented in STATA 10 (StataCorp, College Station, TX). Analyses were carried out for total IS, by stroke subtype and by age of stroke onset (≤ 50 yrs, 50-70 yrs, and ≥ 70 yrs).

With our total sample size (6,865 cases), we had 80% power to detect odds ratios of 1.09 ~ 1.14 for overall IS and odds ratios of 1.20-1.32 for major stroke subtypes (~1,000 cases) for variants with allele frequency 10-50% (Bonferroni-corrected $\alpha = 0.0045 = 0.05/11$ SNPs). In this report, nominal p-values were provided for all the analyses.

Results

Study population characteristics

This study included 6,865 cases and 11,395 controls recruited from 9 studies across North America, Europe, Australia and South Asia. Stroke cases ranged in age between 15 to 101 years. Among cases with subtype information available, the three major stroke subtypes, cardioembolic, large artery (atherosclerotic) and small vessel (lacunar), accounted for ~ 20.9% (n = 1,216), 19.6% (n = 1,137) and 18.0% (n = 1,043) of the cases, respectively; the remaining cases were attributed to either "other known causes" (5.6%; n = 324) or "undetermined causes" (35.9%; n = 2,084). The majority of the study participants were of European ancestry with the exception of those enrolled in the RACE study (1890 cases and 4625 controls), which has enrolled participants of South Asian origin. Detailed characteristics of the participating studies are provided in Supplemental Table S3.

Associations of MI/CAD SNPs and overall IS risk

In the total sample, the meta-analysis odds ratios for all 11 SNPs ranged from 0.92 to 1.11 (Table 2). Only two SNPs were nominally associated with IS: rs11206510 at *PCSK9* (OR of

0.92; 95% CI: 0.86-0.99; *P*=0.03; allele T) and rs3184504 at *SH2B3* (OR of 1.11; 95% CI: 1.01-1.21; *P*=0.03; allele T). This association would not have withstood a conservative Bonferroni correction ($\alpha = 0.05/11$, or 0.0045). Although there was no significant evidence for heterogeneity of effect size across studies for rs11206510, the direction of effect was not consistent across studies with ORs ranging from 0.80 (RACE study) to 1.12 (CEDIR study) (Cochran's Q statistic = 8.1, *P* =0.4) (Figure S1). rs3184504, on the other hand, showed significance evidence for heterogeneity (Cochran's Q statistic = 20.9, *P* =0.01) with one study (BRAINS) showing opposite effect as compared with other studies. We also examined the joint effect of these MI/CAD-associated SNPs by testing for association with the genotype scores and found no significant effect for either genotype score 1 or score 2 (OR = 1.02, *P* = 0.2 for both scores). Removing the RACE study, the only study that had participants of South Asian origin, did not change results significantly although the association with rs11206510 and rs3184504 became less significant (OR=0.94, *P*=0.10 and 1.10, *P*=0.06, respectively) (Supplementary Table S4).

We further stratified the associations between MI/CAD-associated SNPs and overall IS according to age of stroke onset: early ($\leq$ 50 yrs), intermediate (50 yrs < age < 70 yrs) and late onset (age $\geq$ 70 yrs). None of the associations were statistically significant in the age-stratified analyses, either (Supplemental Table S5).

Associations with major ischemic stroke subtypes

We next examined the effects of MI/CAD-associated SNPs on TOAST-defined subtypes (Table 3). Nominally significant associations ($0.03 < p < 0.05$) were observed for four of the different TOAST subtypes. The MI/CAD-associated risk allele at rs9818870 in *MRAS* was

associated with the cardioembolic stroke subtype (OR= 1.17, 95% C.I.: 1.02-1.35; P=0.03); the MI-associated risk allele at rs17465637 in *MIA3* was associated with the small vessel stroke subtype (OR=1.12, 95% C.I.: 1.00-1.26; P=0.05); and the MI-associated risk allele at rs3184504 in *SH2B3* was associated with strokes due to other known causes (OR=1.33, 95% C.I.: 1.02-1.72; P=0.04). In addition, rs11206510 was associated with strokes due to other undetermined causes, although the allele conferring protection against MI was associated with stroke risk (OR = 0.86, 95% C.I.: 0.76-0.99; P =0.03). The ASGC study had a much higher OR and a wide confidence interval for rs11206510 association, but this study contributed only 11 cases of undetermined causes in the analysis. Excluding the ASGC study from the meta-analysis resulted in an OR of 0.86 (95% CI: 0.76-0.97, P=0.01) for the association between rs11206510 and undetermined causes of stroke. The *ANRIL* rs4977574 SNP was very modestly (and not significantly) associated with the large artery stroke subtype (OR=1.09, 95% C.I.: 0.99-1.20; P=0.09), nor was it associated with any other stroke subtype. None of these results withstand correction for multiple testing. Forest plots showing the most strongly associated SNP with each subtype are in Figure S2.

Discussion

It is of interest to consider whether common loci influence susceptibility to MI/CAD and stroke to the extent that such loci could elucidate common genetic and/or biologic pathways. Given that the 11SNPs tested in this study were associated with MI/CAD in previous GWA studies, they likely are among the common SNPs having the largest effect sizes. The risk alleles at these loci were associated with increases of 12-20% in MI risk, with the exception of rs4977574 in *ANRIL*, for which the risk allele was associated with a 28% increase in Europeans

[7, 8, 13]. In contrast, none of the MI/CAD risk alleles at these loci were significantly associated with risk of overall IS, with the estimated odds ratios ranging from 0.92 to 1.11 (i.e., 8% reduction to 11% increase in odds of stroke per allele).

It is possible that failure to detect associations of these SNPs with the combined IS endpoint might be partially attributable to the heterogeneity of the IS phenotype. The large size of our sample provided us with the opportunity to evaluate the association of these SNPs to subtypes of ischemic stroke. Similar to the combined IS endpoint, we did not find any significant associations of MI/CAD SNPs (or the joint genotyping risk scores) with any of the stroke subtypes. Given that this study included more than 6,800 total cases and more than 1,000 cases for the major stroke subtypes, we have sufficient power to detect even small effects on overall stroke although more modest power to detect associations with stroke subtype. Therefore, our findings suggest that these MI/CAD-associated SNPs do not have effects of similar magnitude on overall stroke as they do on MI/CAD. If an association does exist, it is likely to be very modest for overall IS or restricted to a single stroke subtype.

Although the SNP associations with stroke subtypes did not reach statistical significance, it is interesting that the strongest associations we observed in the subtype analysis were genes involved in cell regulation or signaling. For example, the strongest association with cardioembolic stroke was the MI-risk allele at rs9818870 in *MRAS* (OR= 1.17, P=0.03). *MRAS*, an intracellular signal transducer, is highly expressed in the cardiovascular system, and may be involved in cell adhesion [7, 8, 16]. The strongest association with small vessel stroke was the MI-risk allele at rs17465637 in *MIA3* (OR=1.12, P=0.05), which encodes melanoma inhibitory activity 3 and is associated with cell adhesion and migration in inflammatory pathways[17] . It should also be noted that rs4977574 near *ANRIL* was very modestly associated with the large

artery subtype (OR=1.09, P=0.09). Although the association did not achieve statistical significance in our study, other SNPs in the *ANRIL* region on chromosome 9p21 have previously been associated with large artery stroke, with the strongest signal found with SNP rs1537378 (OR=1.21, 95% CI: 1.09-1.35, P=0.0005)[14]. Interestingly, rs1537378 is not in high LD with our target SNP rs4977574 (r^2=0.5), suggesting these 2 SNPs may represent different association signals or each of them may be tagging the causal variant imperfectly (assuming the association is indeed true). *ANRIL* encodes an antisense noncoding RNA that may disrupt other genes in the region, including *CDKN2A and CDKN2B*, two genes that play a key role in regulating cell proliferation, senescence, and apoptosis. We also observed the MI-associated risk allele at rs3184504 in *SH2B3* to be nominally significantly associated with strokes due to other known causes (OR=1.33, 95% C.I.: 1.02-1.72; P=0.04). It has been hypothesized that this SNP could reduce the anti-inflammatory activity of *SH2B3*, which is expressed in the vasculature, thereby leading to the development of plaque development and/or progression in coronary arteries[13].

In contrast, SNPs whose effects on MI are likely to be mediated though lipid metabolism, e.g., rs1122608 at *SMARCA4/LDLR* (19p13), rs646776 at the *CELSR2/PSRC1/SORT1* locus (1p13) and rs11206510 at PCSK9 (1p32), have minimal effects on IS or any of its subtypes, and in some cases, even showed opposite effects on stroke. For example, the MI/CAD-associated risk allele of rs11206510 at *PCSK9*, a gene involved in cholesterol homeostasis, was modestly associated with decreased risk of overall stroke (OR=0.92, P=0.03) or strokes due to undetermined causes (OR=0.86, P=0.03). Our analyses suggest that genes involved in lipid metabolism do not predispose individuals to increased stroke risk as they do for MI although replications will be needed to confirm these associations.

Taken together, our results suggest that the major common loci associated with MI/CAD risk do not have large effects on stroke. However, although our analyses did not reveal any significant associations between MI/CAD SNPs and stroke, the chromosomal regions harboring these loci might still contain stroke-related SNPs that are not in high LD with the MI-associated SNPs, as the example of chromosome 9p region[14]. A limitation of our meta-analysis is that all included studies are case-control-based and some have included recurrent stroke, thus allowing for the possibility of selection toward milder strokes (due to survival bias). It is possible that these genetic MI/CAD variants could be associated with more severe forms of stroke, but longitudinal studies that follow healthy cohorts for stroke occurrence prospectively would be needed to address this issue. Finally, our analyses were based on 11 SNPs unequivocally associated with MI and/or CAD identified from the first wave of meta-analyses for these traits. A second wave of even larger meta-analyses of these traits is in progress that will likely generate additional associations. We can expect most of these newly associated SNPs to have even smaller effect sizes on MI and CAD. In fact, in September 2011, 17 additional CAD-associated SNPs were identified by even larger meta-analyses, and the reported effect sizes for these newly identified SNPs, as expected, were smaller (ranging from 1.06-1.17) than the original 11 SNPs used in the present analysis[18-21]. But this does not necessarily mean that these SNPs will have smaller effect sizes on stroke. Indeed, it is very possible that such SNPs may be in gene pathways that are more relevant to stroke than are the pathways associated with the currently known MI SNPs. Thus, it will be important to monitor new SNPs identified, even those with small effect sizes, as they may generate new biological insights into the etiology of stroke.

Summary

Common variants previously associated with MI/CAD risk do not have effects of similar magnitude on overall IS, but do not preclude moderate associations restricted to specific IS subtypes.

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Disclosures

None

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Table 1. Previous published SNPs that were associated with MI or CAD

SNP	Non-risk/ risk allele*	Frequency of risk allele	Region	Position	Reported gene	Previous reported odds ratio on MI	Reference
rs11206510	C/T	0.81	1p32	55,268,627	PCSK9	1.15	[8]
rs646776	C/T	0.81	1p13	109,620,053	CELSR2-PSRC1-SORT1	1.17	[8, 10]
rs17465637	A/C	0.72	1q41	220,890,152	MIA3	1.13	[8, 12]
rs6725887	T/C	0.14	2q33	203,454,130	WDR12	1.17	[8]
rs9818870	C/T	0.16	3q22.2	139,604,812	MRAS	1.15	[7]
rs12526453	G/C	0.65	6p24	13,035,530	PHACTR1	1.12	[8]
rs4977574	A/G	0.56	9p21	22,088,574	ANRIL/CDKN2B-AS1	1.28	[8, 9, 11]
rs1746048	T/C	0.84	10q11	44,095,830	CXCL12	1.14	[8, 12]
rs3184504	C/T	0.39	12q24	110,368,991	SH2B3	1.13	[13]
rs1122608	T/G	0.75	19p13	11,024,601	SMARCA4-LDLR	1.15	[8]
rs9982601	C/T	0.13	21q22	34,520,998	SLC5A3-MRPS6-KCNE2	1.20	[8]

* Risk allele is the allele associated with increased risk of MI or CAD

Table 2. Association results of the 11 MI/CAD-risk loci and risk scores with ischemic stroke

SNP	MI/CAD-risk allele	Heterogeneity between studies		Association with overall IS		Minimal OR detectable in current study†
		Q (P-value)	I^2, %	OR (95% CI) *	*P*	
rs11206510	T	8.12 (0.42)	1.53	0.92 (0.86, 0.99)	0.03	1.13
rs646776	T	9.02 (0.34)	11.34	0.95 (0.89, 1.01)	0.12	1.13
rs17465637	C	3.09 (0.93)	0	1.03 (0.97, 1.09)	0.37	1.11
rs6725887	C	13.38 (0.06)	47.67	1.03 (0.90, 1.16)	0.69	1.13
rs9818870	T	5.45 (0.61)	0	1.03 (0.95, 1.11)	0.47	1.12
rs12526453	C	8.81 (0.36)	9.2	1.00 (0.95, 1.06)	0.92	1.10
rs4977574	G	4.17 (0.84)	0	1.02 (0.97, 1.07)	0.54	1.09
rs1746048	C	5.37 (0.72)	0	1.03 (0.96, 1.10)	0.38	1.14
rs3184504	T	20.87 (0.01)	61.67	1.11 (1.01, 1.21)	0.03	1.09
rs1122608	G	6.31 (0.61)	0	1.00 (0.95, 1.06)	0.92	1.11
rs9982601	T	6.20 (0.52)	0	1.00 (0.93, 1.09)	0.95	1.13
score1	n/a	12.31 (0.09)	43.15	1.02 (0.99, 1.05)	0.23	n/a

score2	n/a	14.44 (0.04)	51.52	1.02 (0.99, 1.06)	0.23	n/a

OR: odds ratio; CI: confidence interval; n/a: not applicable; *P*: p-value

[*] OR: odds ratios reflects the effect of the MI-associated risk allele with the previously published MI non-risk allele as the reference allele defined in Table 1.

† The minimal odds ratios that current sample size (6,865 overall IS cases) can detect with at least 80% power (α=0.0045).

Table 3. Association results of the 11 MI/CAD-risk loci and risk scores with ischemic stroke, by TOAST subtypes

	Cardioembolic (n=1,216)		Large Artery (n=1,137)		Small Vessel (n=1,043)		Other Known Causes (n=324)		Undetermined causes (n=2,087)	
SNP	OR (95% CI)*	*P*	OR (95% CI)*	*P*	OR (95% CI)*	*P*	OR (95% CI)*	*P*	OR (95% CI)*	*P*
rs11206510	1.02 (0.89, 1.18)	0.78	0.91 (0.80, 1.04)	0.17	1.05 (0.91, 1.21)	0.50	0.89 (0.72, 1.11)	0.32	0.86 (0.76, 0.99)	0.03
rs646776	0.93 (0.83, 1.05)	0.25	0.91 (0.81, 1.03)	0.12	0.95 (0.84, 1.07)	0.38	1.01 (0.78, 1.31)	0.94	0.93 (0.82, 1.05)	0.24
rs17465637	1.01 (0.89, 1.16)	0.86	0.98 (0.87, 1.09)	0.69	1.12 (1.00, 1.26)	0.05	0.96 (0.79, 1.17)	0.69	1.01 (0.92, 1.10)	0.90
rs6725887	0.98 (0.83, 1.16)	0.84	1.01 (0.85, 1.19)	0.93	0.91 (0.76, 1.09)	0.30	1.45 (0.93, 2.26)	0.10	0.96 (0.83, 1.11)	0.58
rs9818870	1.17 (1.02, 1.35)	0.03	0.97 (0.83, 1.13)	0.66	0.91 (0.77, 1.07)	0.24	1.32 (0.92, 1.89)	0.13	0.99 (0.87, 1.12)	0.90

rs12526453	1.06		0.93		0.90		1.03		1.00	
	(0.95, 1.18)	0.31	(0.83, 1.03)	0.15	(0.80, 1.02)	0.09	(0.85, 1.25)	0.74	(0.91, 1.09)	0.99
rs4977574	1.02		1.09		1.03		0.91		1.01	
	(0.89, 1.17)	0.82	(0.99, 1.20)	0.09	(0.94, 1.14)	0.52	(0.69, 1.18)	0.47	(0.94, 1.09)	0.72
rs1746048	0.99		1.05		1.01		0.97		1.00	
	(0.88, 1.12)	0.93	(0.92, 1.2)	0.44	(0.86, 1.18)	0.94	(0.70, 1.33)	0.85	(0.91, 1.1)	0.96
rs3184504	1.05		1.16		1.03		1.33		1.12	
	(0.91, 1.22)	0.51	(0.96, 1.39)	0.11	(0.89, 1.20)	0.68	(1.02, 1.72)	0.04	(0.98, 1.27)	0.11
rs1122608	0.98		1.06		1.03		1.03		0.99	
	(0.88, 1.09)	0.67	(0.95, 1.18)	0.33	(0.92, 1.15)	0.66	(0.85, 1.26)	0.75	(0.91, 1.07)	0.74
rs9982601	1.05		1.04		1.06		1.15		1.02	
	(0.89, 1.25)	0.55	(0.89, 1.22)	0.63	(0.88, 1.27)	0.55	(0.83, 1.60)	0.39	(0.85, 1.22)	0.85
score1	1.02		1.02		1.01		1.06		1.00	
	(0.98, 1.07)	0.29	(0.97, 1.06)	0.47	(0.95, 1.07)	0.85	(0.98, 1.14)	0.16	(0.96, 1.04)	0.97
score2	1.04		1.01		1.00		1.08		1.00	
	(0.99, 1.08)	0.11	(0.96, 1.08)	0.63	(0.94, 1.07)	0.91	(1.01, 1.17)	0.03	(0.96, 1.05)	0.92

n: number of cases; OR: odds ratio; P: p-value

* OR: odds ratio reflects the effect of the MI-associated risk allele with the previously published MI non-risk allele as the reference allele defined in Table 1.